(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 317 148 B1**

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **17.02.93**

(51) Int. Cl.5: **C07D 493/22**, C07H 19/01, A61K 31/365, A61K 31/70, A01N 43/90, C12P 17/08, C12P 19/62, //(C07D493/22, 313:00,311:00,311:00,307:00), (C12P17/08,C12R1:465), (C12P19/62,C12R1:465)

(21) Application number: **88310458.0**

(22) Date of filing: **07.11.88**

The file contains technical information submitted after the application was filed and not included in this specification

(54) Antiparasitic agents.

(30) Priority: **14.11.87 GB 8726730**

(43) Date of publication of application:
24.05.89 Bulletin 89/21

(45) Publication of the grant of the patent:
17.02.93 Bulletin 93/07

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(56) References cited:
EP-A- 0 002 615
EP-A- 0 214 731
EP-A- 0 235 085
EP-A- 0 319 142
FR-A- 2 387 231
GB-A- 2 170 499

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EP 0 317 148 B1

Description

This invention relates to antiparasitic agents and in particular to compounds related to the avermectins and milbemycins but having a novel substituent group at the 25-position and to a process for their preparation.

The avermectins are a group of broad spectrum antiparasitic agents referred to previously as the C-076 compounds. They are produced by fermenting a strain of the microorganism Streptomyces avermitilis ATCC 31267, 31271 or 31272 under aerobic conditions in an aqueous nutrient medium containing inorganic salts and assimilable sources of carbon and nitrogen. The morphological and cultural properties of the strains ATCC 31267, 31271 and 31272 are described in detail in British Patent Specification no. 1573955 which also describes the isolation and the chemical structure of the eight individual components which make up the C-076 complex. The milbemycins are structurally related macrolide antibiotics lacking the sugar residues at the 13-position. They are produced by fermentation, for example as described in British Patent Specification no. 1390336 and European Patent Application publication no. 0170006.

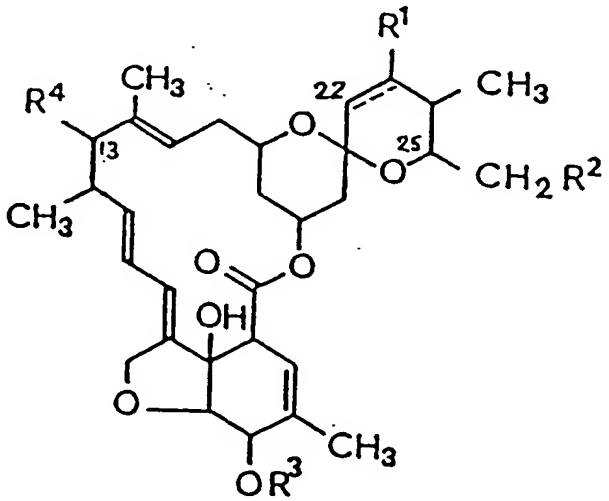
In our European Patent Application publication no. 0214731 we disclose that by adding certain specified carboxylic acids, or derivatives thereof, to the fermentation of an avermectin producing organism it is possible to obtain novel compounds, related to the avermectins but having an unnatural substituent group at the 25-position in place of the isopropyl or sec-butyl group which is normally present.

The novel compounds produced are characterised in that the substituent group at the 25-position is alpha-branched i.e. the carbon atom attached to the C-25 ring position is a secondary carbon atom linked to two further carbon atoms.

In our co-pending U.S. patent application serial no. 6512, corresponding to EP-A-284176 we describe and claim new mutant strains of the microorganism Streptomyces avermitilis lacking branched-chain 2-oxo acid dehydrogenase activity. Said strains have been deposited in the American Type Culture Collection, Rockville, Maryland under the designations Streptomyces avermitilis ATCC 53567 and ATCC 53568.

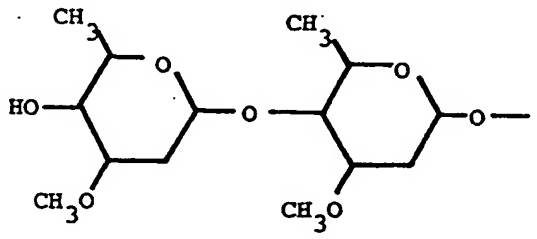
EP-A-235085, FR-A-2387231 and GB-A-2170499 describe milbemycin derivatives prepared by synthesis which may have a methyl or ethyl substituent at the 25-position.

We have now discovered that, by using these new mutant strains of Streptomyces avermitilis it is possible to obtain a further range of novel avermectin derivatives, not previously obtainable, wherein the C-25 substituent is linked by an unbranched (primary) carbon atom. The novel compounds are highly active antiparasitic agents having particular utility as anthelmintics, ectoparasiticides, insecticides and acaricides. The compounds can be subjected to conventional chemical transformation reactions to obtain further novel semi-synthetic derivatives. Thus, according to the present invention there are provided compounds having the formula (I):



wherein the broken line at the 22-23 position represents an optional double bond and wherein either R^1 is H or OH and the double bond is absent, or, the double bond is present and R^1 is absent;
R^2 is H, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, alkoxyalkyl or alkylthioalkyl containing from 1 to 6 carbon atoms in each alkyl or alkoxy group, wherein any of said alkyl, alkoxy alkenyl or alkynyl groups may be

substituted by one or more halo atoms; or a C_3-C_8 cycloalkyl or C_5-C_8 cycloalkenyl group, either of which may optionally be substituted by methylene or one or more C_1-C_4 alkyl groups or halo atoms; or a group of the formula SR^5 wherein R^5 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, C_5-C_8 cycloalkenyl, phenyl or substituted phenyl wherein the substituent is C_1-C_4 alkyl, C_1-C_4 alkoxy or halo;
R^3 is hydrogen or methyl;
and R^4 is H or a 4'-(alpha-L-oleandrosyl)-alpha-L-oleandrosyloxy group of the formula:



with the proviso that when R^1 is H and the double bond is absent or R^4 is H, R^1 is OH and the double bond is absent, R^2 is not H or CH_3.

In the above definition, alkyl groups containing 3 or more carbon atoms may be straight or branched chain. Halo means fluoro, chloro, bromo or iodo.

The C-076 complex comprises eight distinct but closely related compounds described as C-076 A1a, A1b, A2a, A2b, B1a, B1b, B2a and B2b. The "a" series of compounds refers to the natural avermectin wherein the 25-substituent is (S)-sec-butyl and the "b" series to those wherein the 25-substituent is isopropyl. The designations "A" and "B" refer to avermectins wherein the 5-substituent is methoxy or hydroxy, respectively, and the numeral "1" refers to avermectins wherein a double bond is present at the 22-23 position, and numeral "2" to avermectins having a hydrogen at the 22-position and hydroxy at the 23 position.

In this application, the "a" and "b" identifiers have been dropped. Identifiers A1, A2, B1 and B2 have been retained to refer to non-natural avermectins having the structural features corresponding to those of the natural avermectins as noted above.

Preferred compounds of the formula (I) are those wherein R^4 is 4'-(alpha-L-oleandrosyl)-alpha-L-oleandrosyloxy.

Also preferred are compounds of the formula (I) wherein R^2 is SR^5 and R^5 is methyl or ethyl.

In another group of preferred compounds R^2 is methyl, isopropyl or sec-butyl.

In a further group of preferred compounds R^2 is branched C_3-C_8 alkyl group substituted by one or more halo atoms, particularly 1-(trifluoromethyl)ethyl.

In accordance with the invention the compounds of formula (I) wherein R^1 is OH and the double bond is absent or wherein the double bond is present and R^1 is absent and R^4 is 4'-(alpha-L-oleandrosyl)-alpha-L-oleandrosyloxy are prepared by fermenting a Streptomyces avermitilis mutant organism ATCC 53567 or 53568, as described in U.S. patent application serial no. 6212, in the presence of the appropriate carboxylic acid of the formula $R^2CH_2CO_2H$, wherein R^2 is as previously defined, or a salt, ester, or amide thereof or oxidative precursor therefor. The acid is added to the fermentation either at the time of inoculation or at intervals during the fermentation. Production of the compounds of formula (I) may be monitored by removing samples from the fermentation, extracting with an organic solvent and following the appearance of the compound of formula (I) by chromatography, for example using high pressure liquid chromatography. Incubation is continued until the yield of the compound of formula (I) has been maximised, generally for a period of from 12 to 16 days.

A preferred level of each addition of the carboxylic acid or derivative thereof is between 0.05 and 4.0 grams per litre. The best yields of the compounds of formula (I) are obtained by gradually adding the acid to the fermentation, for example by daily additions of the acid or derivative thereof over a period of several days. The acid may be added as a salt, such as the sodium or ammonium salt, or as an ester, such as the methyl or ethyl ester or as an amide, but is preferably added as the free acid. Alternative substrates which may be used in the fermentation are derivatives which are oxidative precursors for the carboxylic acids; thus, for example suitable substrates would be alcohols of the formula $R^2(CH_2)_nOH$ or amine derivatives of the formula $R^2(CH_2)_nNH_2$, wherein n is 2, 4 or 6, substituted lower alkanoic acids of the formula $R^2(CH_2)_nCO_2H$ wherein n is 3 or 5 or aldehydes of the formula $R^2(CH_2)_nCHO$ wherein n is 1, 3 or 5 and R^2 is as

previously defined. The media used for the fermentation may be a conventional complex media containing assimilable sources of carbon, nitrogen and other trace elements.

After fermentation for a period of several days at a temperature preferably in the range of from 24 to 33 °C, the fermentation broth is centrifuged or filtered and the mycelial cake is extracted with acetone or methanol. The solvent extract is concentrated and the desired product is then extracted into a water-immiscible organic solvent, such as methylene chloride, ethyl acetate, chloroform, butanol or methyl isobutyl ketone. The solvent extract is concentrated and the crude product containing the compounds of formula (I) is further purified as necessary by chromatography, for example using preparative reverse phase, high pressure liquid chromatography.

The product is generally obtained as a mixture of the compounds of formula (I) wherein R^4 is 4′-(alpha-L-oleandrosyl)-alpha-L-oleandrosyloxy, R^1 is OH and the double bond absent or R^1 is absent and the double bond is present and wherein R^3 is H or CH_3; however the proportions can vary depending on the particular carboxylic acid employed and the conditions used in the fermentation.

We have found that a range of carboxylic acids as defined by $R^2CH_2CO_2H$ may be added to the fermentation to yield avermectins having a novel substituent group at the 25-position. Examples of particular acids which may be employed include the following:

methylthioacetic acid
ethylthioacetic acid
3-methylbutyric acid
3-trifluoromethyl butyric acid
3-methylpentanoic acid
n-butyric acid
cyclopentane acetic acid
thiophene-3-acetic acid

and propionic acid.

In one particular and preferred aspect of the invention, the fermentation is performed in the presence of methylthioacetic acid to yield predominantly the compound of formula (I) wherein R^1 is OH, the double bond is absent, R^2 is SCH_3, R^3 is CH_3 and R^4 is 4′-(alpha-L-oleandrosyl)-alpha-4-oleandrosyloxy, referred to herein as 25-methylthiomethyl avermectin A2.

In another preferred aspect of the invention, the fermentation is performed in the presence of propionic acid to yield predominantly the compound of formula (I) wherein R^1 is OH, the double bond is absent, R^2 is CH_3, R^3 is CH_3 and R^4 is 4′(-(alpha-L-oleandrosyl)-alpha-4-oleandrosyloxy, referred to herein as 25-ethyl avermectin A2.

In a further preferred aspect of the invention the fermentation is performed in the presence of 3-methylbutyric acid to yield predominantly the compound of formula (I) wherein R^1 is absent, the double bond is present, R^2 is isopropyl, R^3 is H and R^4 is 4′-(alpha-L-oleandrosyl)-alpha-4-oleandrosyloxy, referred to herein as 25-isobutyl avermectin B1.

In a further preferred aspect of the invention, the fermentation is performed in the presence of 3-trifluoromethyl butyric acid to yield predominantly the compounds of formula (I) wherein R^1 is OH, the double bond is absent, R^2 is 1-(trifluoromethyl)ethyl, R^4 is 4′-(alpha-L-oleandrosyl)alpha-4-oleandrosyloxy and R^3 is CH_3 or H, referred to herein as 25-(2-trifluoromethylpropyl)avermectin A2 and B2 respectively.

Compounds of the formula (I) wherein the double bond is present and R^1 is absent may alternatively be prepared from the corresponding compound of formula (I) wherein R^1 is OH and the double bond is absent by a dehydration reaction. The reaction is performed by first selectively protecting the hydroxyl groups at the 5 and 4″ positions, e.g. as the t-butyldimethylsilyloxy acetyl derivative, then reacting with a substituted thiocarbonyl halide, such as (4-methylphenoxy)thiocarbonyl chloride, followed by heating in a high boiling point solvent, e.g. trichlorobenzene, to effect the dehydration. The product is finally deprotected to give the unsaturated compound. These steps together with appropriate reagents and reaction conditions are described in United States patent 4328335.

The compounds of formula I wherein R^3 is H may also be prepared from the corresponding compounds wherein R^3 is CH_3 by demethylation. This reaction is achieved by treating the 5-methoxy compound, or a suitably protected derivative thereof, with mercuric acetate and hydrolysing the resulting 3-acetoxy enol ether with dilute acid to give the 5-keto compound. This is then reduced using, for example, sodium borohydride to yield the 5-hydroxy derivative. Appropriate reagents and reaction conditions for these steps are described in United States patent 4423209.

The compounds of formula I wherein R^1 is H and the double bond is absent can be prepared from the corresponding compound wherein the double bond is present and R^1 is absent, by selective catalytic hydrogenation using an appropriate catalyst. For example the reduction may be achieved using tris-

(triphenylphosphine)rhodium (I) chloride as described in European patent application publication no. 0001689.

The compounds of formula (I) wherein R^4 is H are prepared from the corresponding compounds wherein R^4 is 4′-(alpha-L-oleandrosyl)-alpha-L-oleandrosyloxy by removing the 4′-(alpha-L-oleandrosyl)-alpha-L-oleandrose group by mild hydrolysis with an acid in an aqueous organic solvent to yield the aglycone having a hydroxy group at the 13-position; this is then halogenated, for example by reaction with a benzene sulphonyl halide, to yield the 13-deoxy-13-halo derivative which is finally selectively reduced, for example using tributyltin hydride. In order to avoid unwanted side reactions it is desirable to protect any other hydroxy groups which may be present, for example using a tert-butyldimethylsilyl group. This is then readily removed after the halogenation or reduction step by treatment with methanol containing a trace of acid. All these steps together with appropriate reagents and reaction conditions for their performance are described in European patent application publication no. 0002615.

The compounds of the invention are highly active antiparasitic agents having particular utility as anthelmintics, ectoparasiticides, insecticides and acaricides.

Thus the compounds are effective in treating a variety of conditions caused by endoparasites including, in particular, helminthiasis which is most frequently caused by a group of parasitic worms described as nematodes and which can cause severe economic losses in swine, sheep, horses and cattle as well as affecting domestic animals and poultry. The compounds are also effective against other nematodes which affect various species of animals including, for example, Dirofilaria in dogs and various parasites which can infect humans including gastro-intestinal parasites such as Ancylostoma, Necator, Ascaris, Strongyloides, Trichinella, Capillaria, Trichuris, Enterobius and parasites which are found in the blood or other tissues and organs such as filiarial worms and the extra intestinal stages of Strongyloides and Trichinella.

The compounds are also of value in treating ectoparasite infections including in particular arthropod ectoparasites of animals and birds such as ticks, mites, lice, fleas, blowfly, biting insects and migrating dipterous larvae which can affect cattle and horses.

The compounds are also insecticides active against household pests such as the cockroach, clothes moth, carpet beetle and the housefly as well as being useful against insect pests of stored grain and of agricultural plants such as spider mites, aphids, caterpillars and against migratory orthopterans such as locusts.

The compounds of formula (I) are administered as a formulation appropriate to the specific use envisaged and to the particular species of host animal being treated and the parasite or insect involved. For use as an anthelmintic the compounds may be administered orally in the form of a capsule, bolus, tablet or preferably a liquid drench, or alternatively, they may be administered by injection or as an implant. Such formulations are prepared in a conventional manner in accordance with standard veterinary practice. Thus capsules, boluses or tablets may be prepared by mixing the active ingredient with a suitable finely divided diluent or carrier, additionally containing a disintegrating agent and/or binder such as starch, lactose, talc, magnesium stearate etc. A drench formulation may be prepared by dispersing the active ingredient in an aqueous solution together with dispersing or wetting agents etc. and injectable formulations may be prepared in the form of a sterile solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. These formulations will vary with regard to the weight of active compound depending on the species of host animal to be treated, the severity and type of infection and the body weight of the host. Generally for oral administration a dose of from about 0.001 to 10 mg per Kg of animal body weight given as a single dose or in divided doses for a period of from 1 to 5 days will be satisfactory but of course there can be instances where higher or lower dosage ranges are indicated and such are within the scope of this invention.

As an alternative the compounds may be administered with the animal feedstuff and for this purpose a concentrated feed additive or premix may be prepared for mixing with the normal animal feed.

For use as an insecticide and for treating agricultural pests the compounds are applied as sprays, dusts, emulsions and the like in accordance with standard agricultural practice.

For human use the compounds are administered as a pharmaceutically acceptable formulation in accordance with normal medical practice.

The invention is illustrated by the following Examples in which Examples 1 to 8 are Examples of the preparation of compounds of the formula (I), Example 9 is an example of a drench formulation and Examples 10 and 11 illustrate the antiparasitic and insecticidal activity of the compounds.

EXAMPLE 1

25-Ethyl avermectin A2

A frozen inoculum (2 ml) of a culture of Streptomyces avermitilis mutant organism ATCC 53568 was inoculated into 50 mls of a medium containing starch (1 g), Pharmamedia (Trademark) (0.75 g), ardamine pH (0.25 g), and calcium carbonate (0.1 g) in a 300 ml flask and incubated at 28°C for 2 days. This inoculum (50 ml) was transferred to a second inoculum flask (1 litre) containing starch (20 g), Pharmamedia (15 g), ardamine pH (5 g) and calcium carbonate (2 g) and incubated at 28°C for a further 2 days. This inoculum was used to inoculate 60 litres of a medium containing starch (6 kg), magnesium sulphate (60 g), Pharmamedia (300 g), dipotassium hydrogen phosphate (60 g), ferrous sulphate (0.6 g), calcium carbonate (420 g), glutamic acid (36 g), zinc sulphate (0.06 g) and manganous sulphate (0.06 g) contained in a 60 litre fermenter. The fermentation was incubated at 29°C, with agitation at 350 r.p.m. and aeration at 60 litres per minute. Sodium propionate (140 g) was added after 96 hours and again after 192 hours (54 g). After 288 hours the mycelium was removed by filtration and extracted with acetone (2 x 50 litres) followed by ethyl acetate (50 litres). The acetone extract was concentrated to approximately 10 litres and extracted with the above ethyl acetate extract in three portions. The resulting ethyl acetate layers were combined and evaporated to give a brown oil (112 g).

The above oil was dissolved in 160 ml of a mixture of methanol and water (95:5) and extracted with n-hexane (2 x 300 ml), the hexane extracts were discarded and the methanol layer was evaporated to give a brown oil (87 g). The latter was dissolved in methylene chloride (250 ml) and stirred with silica gel (80 g) and charcoal (30 g) for 1 hour. The silica and charcoal were removed by filtration through Arbacel and the filtrate was evaporated to give a yellow oil (53 g). The latter was dissolved in methylene chloride (2.2 litres) and stirred with alumina (190 g) for two hours. The alumina was removed by filtration and the filtrate stirred with more alumina (64 g) for a further hour. The alumina was removed by filtration and the combined filter cakes from both filtrations were stirred with chloroform (1.3 litres) for 45 minutes and then the alumina was removed by filtration. The filtrate was evaporated to give a pale yellow oil (12.5 g) which was dissolved in diethyl ether and added to a column of silica gel (400 g). The column was eluted with diethyl ether and 100 ml fractions were collected. Fractions 21-28 were combined and the solvent evaporated to yield partially purified material (150 mg). The product was dissolved in methanol (0.5 ml) and chromatographed on a C18 Zorbax ODS (Trademark, Dupont) column (21 mm x 25 cm) eluting with a mixture of methanol and water (77:23) at a flowrate of 9 mls. per minute. The relevant fractions were combined and the solvent evaporated to yield the compound of formula (I) wherein R^1 is OH, the double bond is absent, R^2 and R^3 are both CH_3 and R^4 is 4′-(alpha-L-oleandrosyl)-alpha-L-oleandrosyloxy as a white powder, m.p 146-153°C. The structure of the product was confirmed by fast atom bombardment mass spectrometry, performed on a VG Model 7070E mass spectrometer using a sample matrix of triethylene glycol with solid sodium chloride. $(M + Na)^+$ observed at m/e 899 (theoretical 899).

Electron impact mass spectrometry was performed using a VG Model 7070F mass spectrometer. The m/e values for the principal fragments were: 570, 295, 277, 275, 183, 165, 145, 127, 113, 95 and 87.

EXAMPLE 2

25-Methylthiomethyl avermectin A2

A frozen inoculum (2 ml) of a culture of Streptomyces avermitilis mutant organism ATCC 53568 was inoculated into 50 mls of a medium containing starch (1 g), Pharmamedia (Trademark) (0.75 g), ardamine pH (0.25 g) and calcium carbonate (0.1 g) in a 300 ml flask and incubated for 2 days at 28°C on a reciprocal shaker operating at 180 r.p.m. An inoculum from this flask (25 ml) was transferred to a 3 litre flask containing 600 mls of the above medium (all ingredients pro rata) and was incubated for two days at 28°C with agitation on a reciprocal shaker operating at 180 r.p.m. The product from this flask (40 ml) was used to inoculate a 3 litre fermenter containing 2.5 litres of a medium consisting of starch (250 g), magnesium sulphate (2.5 g). Pharmamedia (12.5 g), dipotassium hydrogen phosphate (2.5 g), ferrous sulphate (0.025 g), calcium carbonate (1.75 g), glutamic acid (1.5 g), zinc sulphate (0.0025 g), and manganous sulphate (1.5 g). This fermentation was incubated at 28°C with agitation at 1000 r.p.m. Methylthioacetic acid (1 g) was added at 96 hours and the fermentation continued for a further 11 days. Then the mycelium was removed by filtration and extracted with acetone (2 x 2 litres) followed by ethyl acetate (2 litres). The acetone extract was concentrated to approximately 400 mls. and extracted with the ethyl acetate extract in three portions. The resulting ethyl acetate layers were combined and evaporated to

give a brown oil (4 g) which was dissolved in diethyl ether and applied to a column of silica gel (100 g). The column was eluted with diethyl ether and 50 ml fractions were collected. Fractions 11-18 were combined and evaporated to yield partially purified material which was further purified by chromatography on a C18 Zorbax ODS (Trademark, Dupont) column (21 mm x 25 cm) eluting with a mixture of methanol and water (77:23) at a flowrate of 9 mls. per minute. The relevant fractions were combined and evaporated to yield the compound of formula (I) wherein R^1 is OH, the double bond is absent, R^2 is SCH_3, R^3 is CH_3 and R^4 is 4′-(alpha-L-oleandrosyl)-alpha-L-oleandrosyloxy as a white powder m.p. 105-112°C. The structure of the product was confirmed by fast atom bombardment mass spectrometry was performed on a VG Model 7070E mass spectrometer using a sample matrix of triethylene glycol with solid sodium chloride. $(M + Na)^+$ observed at m/e 931 (theoretical 931).

Electron impact mass spectrometry was performed using a VG Model 7070F mass spectrometer. The m/e values for the principal fragments were: 327, 309, 243, 225, 215, 145, 127, 113, 95 and 87.

EXAMPLE 3

25-(2-Trifluoromethyl)propyl avermectins A2 and B2

The procedure of Example 1 was followed but using 3-trifluoromethyl butyric acid as substrate instead of sodium propionate. The relevant combined fractions from silica gel chromatography containing the crude A2 derivative were chromatographed on a C18 Zorbax ODS (Trademark, Dupont) column (21 mm x 25 cm) eluting with a mixture of methanol and water (75:25) at a flowrate of 9 mls/min. Fractions 167-179 were combined and evaporated to yield the compound of formula (I) wherein R^1 is OH, the double bond is absent, R^2 is a 1-(trifluoromethyl)ethyl, R^3 is CH_3 and R^4 is 4′-(alpha-L-oleandrosyl)-L-oleandrosyloxy as a white powder, m.p. 130-136°C. The structure of the product was confirmed by fast atom bombardment mass spectrometry, performed on a VG Model 7070E mass spectrometer using a sample matrix of triethylene glycol with solid sodium chloride. $(M + Na)^+$ observed at m/e 981 (theoretical 981).

Electron impact mass spectrometry was performed using a VG Model 7070F mass spectrometer. The m/e values for the principal fragments were: 652, 377, 359, 293, 275, 265, 257, 247, 223, 179, 145, 127, 113, 111 and 87.

The relevant fractions from silica gel chromatography containing the crude B2 derivative were combined and chromatographed on a C-18 Dynamax (Trademark Rainin) column (41.4 mm x 25 cm) eluting with a mixture of methanol and water (73:27) at a flowrate of 60 mls/min. Relevant fractions were combined to yield the compound of formula (I), wherein R^1 is OH, the double bond is absent, R^2 is 1-(trifluoromethyl)-ethyl, R^3 is H and R^4 is 4′-(alpha-L-oleandrosyl)-L-oleandrosyloxy as a white powder, m.p. 158-160°C. The structure of the product was confirmed by fast atom bombardment mass spectrometry performed on a VG Model 7070E mass spectrometer using a sample matrix of triethylene glycol with solid sodium chloride. $(M + Na)^+$ observed at m/e 967 (theoretical 967).

Electron impact mass spectrometry was performed using a VG Model 7070F mass spectrometer. The m/e values for the principal fragments were: 638, 377, 359, 293, 275, 265, 261, 257, 247, 223, 145, 127, 113, 111, 95 and 87.

EXAMPLE 4

25-Ethylthiomethyl avermectin A2

The procedure of Example 1 was followed but using ethylthioacetic acid as substrate instead of sodium propionate. After chromatography on a Zorbax ODS (Trademark, Dupont) column fractions 24-72 were combined to yield the compound of formula (I) wherein R^1 is OH, the double bond is absent, R^2 is ethylthio, R^3 is CH_3 and R^4 is 4′-(alpha-L-oleandrosyl)-L-oleandrosyloxy as a white powder, m.p. 265-270°C (dec). The structure of the product was confirmed by fast atom bombardment mass spectrometry performed on a VG Model 7070E mass spectrometer using a sample matrix of triethylene glycol with solid sodium chloride. $(M + Na)^+$ observed at m/e 945 (theoretical 945).

Electron impact mass spectrometry was performed using a VG Model 7070F mass spectrometer. The m/e values for the principal fragments were: 616, 473, 341, 323, 257, 239, 229, 211, 187, 179, 145, 113 and 87.

EXAMPLE 5

25-Isobutyl avermectin B1

The procedure of Example 1 was followed but using 3-methylbutyric acid as substrate instead of sodium propionate. The relevant fractions from silica gel chromatography were combined and chromatographed on a C18 Zorbax ODS (Trademark, Dupont) column (21 mm x 25 cm) eluting with a mixture of methanol and water (81:19) at a flowrate of 9 mls/min. Fractions 93-98 were combined and evaporated to yield the compound of formula (I) wherein R^1 is absent, the double bond is present, R^2 is isopropyl, R^3 is H and R^4 is 4′-(alpha-L-oleandrosyl)-L-oleandrosyloxy, as a white powder, m.p. 120-123. The structure of the product was confirmed by fast atom bombardment mass spectrometry performed on a VG Model 7070E mass spectrometer using a sample matrix of triethylene glycol with solid sodium chloride. $(M + Na)^+$ observed at m/e 895 (theoretical 895).

Electron impact mass spectrometry was performed using a VG Model 7070F mass spectrometer. The m/e values for the principal fragments were: 565, 319, 305, 221, 193, 169, 145, 127, 113 and 87.

EXAMPLE 6

25-(2-Methylbutyl) avermectins A2 and B1

The procedure of Example 1 was followed but using 3-methylpentanoic acid as substrate instead of sodium propionate. The relevant fractions from silica gel chromatography containing the crude A2 derivative were combined and chromatographed on a C-18 Zorbax ODS (Trademark Dupont) column (21 mm x 25 cm) eluting with a mixture of methanol and water (80:20) at a flowrate of 9 mls/min. Relevant fractions were combined to yield the compound of formula (I), wherein R^1 is OH, the double bond is absent, R^2 is sec-butyl, R^3 is methyl and R^4 is 4′-(alpha-L-oleandrosyl)-L-oleandrosyloxy as a white powder, m.p. 120-125 °C. The structure of the product was confirmed by fast atom bombardment mass spectrometry performed on a VG Model 7070E mass spectrometer using a sample matrix of triethylene glycol with solid sodium chloride. $(M + Na)^+$ observed at m/e 941 (theoretical 941).

Electron impact mass spectrometry was performed using a VG Model 7070F mass spectrometer. The m/e values for the principal fragments were: 337, 319, 253, 235, 225, 207, 179, 145, 113 and 87.

The relevant fractions from silica gel chromatography containing the crude B1 derivative were combined and chromatographed on a C-18 Ultrasphere (Trademark Beckman) column (10 mm x 25 cm) eluting with a mixture of methanol and water (85:15) at a flowrate of 4 mls/ min. Relevant fractions were combined to yield the compound of formula (I), wherein R^1 is H, the double bond is present, R^2 is sec-butyl, R^3 is H and R^4 is 4′-(alpha-L-oleandrosyl)-L-oleandrosyloxy as a white powder, m.p. 158-164 °C. The structure of the product was confirmed by fast atom bombardment mass spectrometry performed on a VG Model 7070E mass spectrometer using a sample matrix of triethylene glycol with solid sodium chloride $(M + Na)^+$ observed at m/e 909 (theoretical 909).

Electron impact mass spectrometry was performed using a VG Model 7070F mass spectrometer. The m/e values for the principal fragments were: 319, 235, 207, 183, 145, 113, 95 and 87.

EXAMPLE 7

25-n-Propyl avermectin A2

The procedure of Example 1 was followed but using n-butyric acid as substrate instead of sodium propionate. The relevant fractions from silica gel chromatography were combined and chromatographed on a C-18 Dynamax (Trademark Rainin) column (41.4 mm x 25 cm) eluting with a gradient of methanol and water from (75:25) to (100:0) over 170 minutes at a flowrate of 40 mls/min. One minute fractions were collected and fractions 36 and 37 were combined to yield the compound of formula (I), wherein R^1 is OH, the double bond is absent, R^2 is ethyl, R^3 is methyl and R^4 is 4′-(alpha-L-oleandrosyl)-L-oleandrosyloxy as a white powder, m.p. 150-155 °C. The structure of the product was confirmed by fast atom bombardment mass spectrometry performed on a VG Model 7070E mass spectrometer using a sample matrix of triethylene glycol with solid sodium chloride. $(M + Na)^+$ observed at m/e 913 (theoretical 913).

Electron impact mass spectrometry was performed using a VG model 7070 F mass spectrometer. The m/e values for the principal fragments were: 584, 309, 291, 225, 207, 197, 179, 145, 113 and 87.

EXAMPLE 8

25-Cyclopentylmethyl avermectins B1 and B2

The procedure of Example 1 was followed but using cyclopentane acetic acid instead of sodium propionate. The relevant fractions from silica gel chromatography containing the crude B1 derivative were combined and chromatographed on a C-18 Dynamax (Trademark Rainin) column (41.4 mm x 25 cm) eluting with a mixture of methanol and water (84:16) at a flowrate of 60 mls/min. Relevant fractions were combined to yield a compound of formula (I), wherein R^1 is absent, the double bond is present, R^2 is cyclopentyl, R^3 is H and R^4 is 4′-(alpha-L-oleandrosyl)-L-oleandrosyloxy, as a white powder, m.p. 140-146°C. The structure of the product was confirmed by fast atom bombardment mass spectrometry performed on a VG Model 7070E mass spectrometer using a sample matrix of triethylene glycol with solid sodium chloride. $(M + Na)^+$ observed at m/e 921 (theoretical 921).

Electron impact mass spectrometry was performed using a VG Model 7070F mass spectrometer. The m/e values for the principal fragments were: 592, 331, 295, 257, 247, 218, 195, 145, 127, 113, 111, 95 and 87.

The relevant fractions from silica gel chromatogrpahy containing the crude B2 derivative were combined and chromatographed on a C-18 Ultrasphere (Trademark Beckman) column (10 mm x 25 cm) eluting with a mixture of methanol and water (80:20) at a flowrate of 4 mls/min. Relevant fractions were combined to yield the compound of formula (I), wherein R^1 is OH, the double bond is absent, R^2 is cyclopentyl, R^3 is H and R^4 is 4′-(alpha-L-oleandrosyl)-L-oleandrosyloxy as a white powder, m.p. 155-165°C. The structure of the product was confirmed by fast atom bombardment mass spectrometry performed on a VG Model 7070E mass spectrometer using a sample matrix of triethylene glycol with solid sodium chloride. $(M+Na)^+$ observed at m/e 939 (theoretical 939).

Electron impact mass spectrometry was performed using a VG Model 7070F mass spectrometer. The m/e values for the principal fragments were: 349, 335, 331, 289, 265, 261, 257, 247, 237, 219, 195, 179, 145, 127, 113, 111, 95 and 87.

EXAMPLE 9

Drench Formulation

The product of any one of the preceding Examples was dissolved in polyethylene glycol (average molecular weight 300) to give a solution containing 400 micrograms/ml for use as a drench formulation.

EXAMPLE 10

Anthelmintic Activity

Anthelmintic activity was evaluated against Caenorhabditis elegans using the in vitro screening test described by K. G. Simpkin and G. L. Coles in Parasitology, 1979, 79, 19. The products of Examples 1 to 8 all killed 100% of the worms at a well concentration of 0.1 micrograms per ml.

EXAMPLE 11

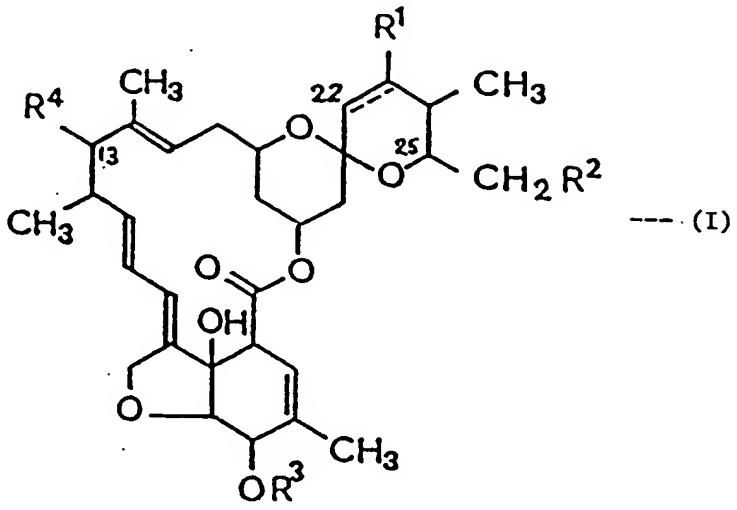
Insecticidal Activity

Activity against the larval stage of the blowfly Lucilia cuprina (Q strain) is demonstrated using a standard procedure in which first instar larvae are kept in contact with filter paper treated with test compound. The test compound is first applied to the paper as an acetone solution. The treated filter papers are then placed into tubes containing 1 ml of newborn calf serum and the first instars are added. The products of Examples 1 to 8 killed 100% of the larvae when applied to the filter paper at a level of 1 milligram per square metre.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A compound having the formula:



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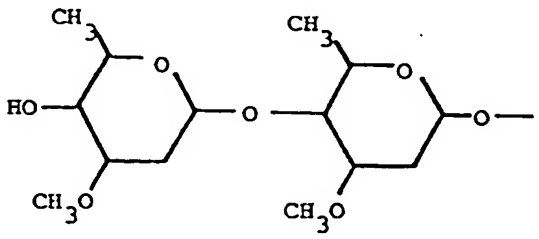
wherein the broken line at the 22-23 position represents an optional double bond and wherein either R^1 is H or OH and the double bond is absent, or, the double bond is present and R^1 is absent;
R^2 is H, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, alkoxyalkyl or alkylthioalkyl containing from 1 to 6 carbon atoms in each alkyl or alkoxy group, wherein any of said alkyl, alkoxy alkenyl or alkynyl groups may be substituted by one or more halo atoms; or a C_3-C_8 cycloalkyl or C_5-C_8 cycloalkenyl group, either of which may optionally be substituted by methylene or one or more C_1-C_4 alkyl groups or halo atoms; or a group of the formula SR^5 wherein R^5 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, C_5-C_8 cycloalkenyl, phenyl or substituted phenyl wherein the substituent is C_1-C_4 alkyl, C_1-C_4 alkoxy or halo;
R^3 is hydrogen or methyl;
and R^4 is H or a 4'-(alpha-L-oleandrosyl)-alpha-L-oleandrosyloxy group of the formula:



with the proviso that when R^1 is H and the double bond is absent, or R^4 is H, R^1 is OH and the double bond is absent, R^2 is not H or CH_3.

2. A compound as claimed in claim 1 wherein R^4 is 4'-(alpha-L-oleandrosyl)-alpha-L-oleandrosyloxy.

3. A compound as claimed in claim 2 wherein R^2 is SR^5 and R^5 is methyl or ethyl.

4. A compound as claimed in claim 2 wherein R^2 is methyl, isopropyl or sec-butyl.

5. A compound as claimed in claim 2 wherein R^2 is 1-(trifluoromethyl)ethyl.

6. A process for preparing a compound of the formula (I) as claimed in claim 1 which comprises fermenting a Streptomyces avermitilis mutant organism ATCC 53567 or 53568, in the presence of the appropriate carboxylic acid of the formula $R^2CH_2CO_2H$, wherein R^2 is as previously defined, or a salt, ester, or amide thereof or oxidative precursor therefor, and isolating the compound of formula I wherein R^1 is OH and the double bond is absent or wherein the double bond is present and R^1 is absent and R^4 is 4'-(alpha-L-oleandrosyl)-alpha-L-oleandrosyloxy and, if desired, hydrogenating the product wherein the double bond is present and R^1 is absent to obtain the compounds of formula (I) wherein the double bond is absent and R^1 is H, or hydrolysing followed by halogenation and reduction to obtain the compounds of formula (I) wherein R^4 is H.

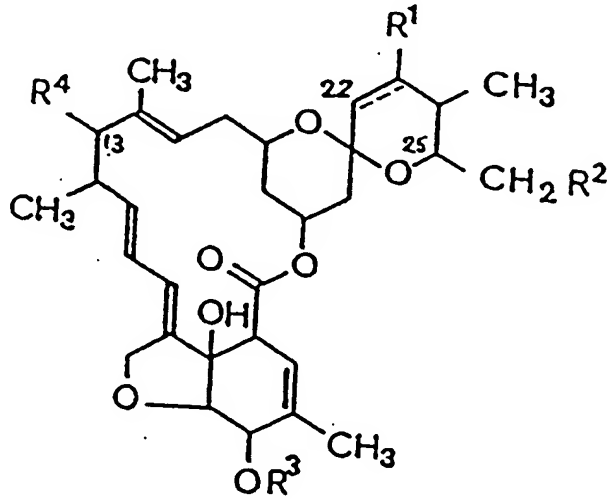
7. A composition for the treatment and prevention of parasitic infections in humans and animals, including ectoparasiticidal, insecticidal, acaricidal and anthelmintic compositions, which comprises a compound of the formula (I) as claimed in any one of claims 1 to 5 together with an inert diluent or carrier.

8. A composition as claimed in claim 7 in the form of a liquid drench or an oral or injectable formulation or in the form of an animal feedstuff or a premix or supplement for addition to animal feed.

9. A compound of the formula I as claimed in any one of claims 1 to 5 for use in the treatment or prevention of parasitic infections in humans and animals.

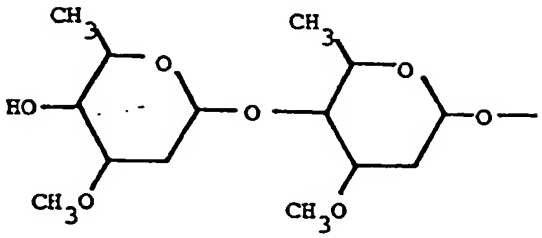
Claims for the following Contracting States : ES, GR

1. A process for preparing a compound having the formula:



--- (I)

wherein the broken line at the 22-23 position represents an optional double bond and wherein either R^1 is H or OH and the double bond is absent, or, the double bond is present and R^1 is absent;
R^2 is H, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, alkoxyalkyl or alkylthioalkyl containing from 1 to 6 carbon atoms in each alkyl or alkoxy group, wherein any of said alkyl, alkoxy alkenyl or alkynyl groups may be substituted by one or more halo atoms; or a C_3-C_8 cycloalkyl or C_5-C_8 cycloalkenyl group, either of which may optionally be substituted by methylene or one or more C_1-C_4 alkyl groups or halo atoms; or a group of the formula SR^5 wherein R^5 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, C_5-C_8 cycloalkenyl, phenyl or substituted phenyl wherein the substituent is C_1-C_4 alkyl, C_1-C_4 alkoxy or halo;
R^3 is hydrogen or methyl;
and R^4 is H or a 4'-(alpha-L-oleandrosyl)-alpha-L-oleandrosyloxy group of the formula:



with the proviso that when R^1 is H and the double bond is absent, or R^4 is H, R^1 is OH and the double bond is absent, R^2 is not H or CH_3 which comprises fermenting a Streptomyces avermitilis mutant organism ATCC 53567 or 53568, in the presence of the appropriate carboxylic acid of the formula $R^2CH_2CO_2H$, wherein R^2 is as previously defined, or a salt, ester, or amide thereof or oxidative precursor therefor, and isolating the compound of formula I wherein R^1 is OH and the double bond is absent or wherein the double bond is present and R^1 is absent and R^4 is 4'-(alpha-L-oleandrosyl)-alpha-L-oleandrosyloxy, and, if desired, hydrogenating the product wherein the double bond is present and R^1 is absent to obtain the compounds of formula (I) wherein the double bond is absent and R^1 is H, or hydrolysing followed by halogenation and reduction to obtain the compounds of formula (I) wherein R^4 is H.

2. A process as claimed in claim 1 wherein R^4 is 4'-(alpha-L-oleandrosyl)-alpha-L-oleandrosyloxy and the optional hydrolysis, halogenation and reduction steps are not performed.

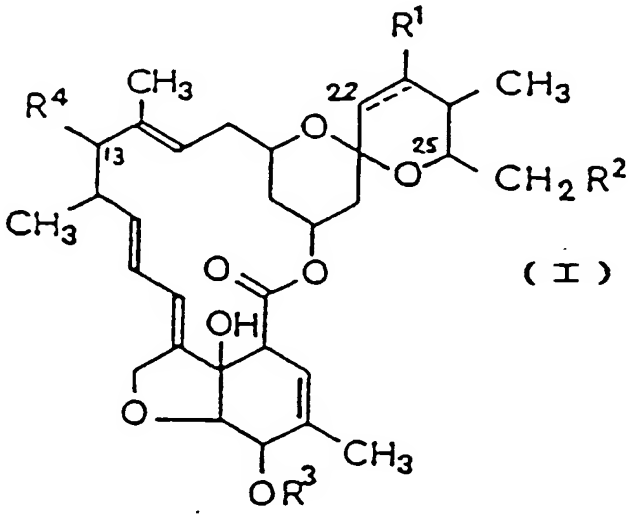
3. A process as claimed in claim 2 wherein R^2 is SR^5 and R^5 is methyl or ethyl.

4. A process as claimed in claim 2 wherein R^2 is methyl, isopropyl or sec-butyl.

5. A process as claimed in claim 2 wherein R^2 is 1-(trifluoromethyl)ethyl.

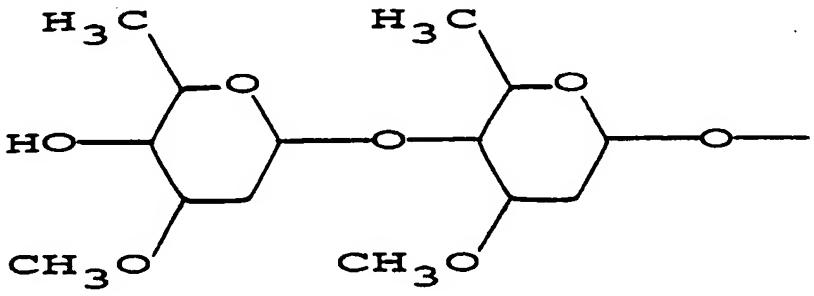
Patentansprüche
Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Verbindung der Formel



worin die gestrichelte Linie in der 22-23-Stellung eine wahlfreie Doppelbindung bedeutet und worin entweder R^1 die Bedeutung H oder OH aufweist und die Doppelbindung fehlt, oder, worin die Doppelbindung vorhanden ist und R^1 fehlt;

R^2 ist H, C_{1-8}-Alkyl, C_{2-8}-Alkenyl, C_{2-8}-Alkinyl, Alkoxyalkyl oder Alkylthioalkyl mit 1 bis 6 Kohlenstoffatomen in jeder Alkyl- oder Alkoxy-Gruppe, worin irgendeine der Alkyl-, Alkoxy-, Alkenyl- oder Alkinyl-Gruppen durch ein oder mehrere Halogenatome substituiert sein kann; oder eine C_{3-8}-Cycloalkyl- oder C_{5-8}-Cycloalkenyl-Gruppe, wobei jede von beiden gegebenenfalls durch Methylen oder eine oder mehrere C_{1-4}-Alkyl-Gruppen oder Halogenatome substituiert sein kann; oder eine Gruppe der Formel SR^5, worin R^5 C_{1-8}-Alkyl, C_{2-8}-Alkenyl, C_{2-8}-Alkinyl, C_{3-8}-Cycloalkyl, C_{5-8}-Cycloalkenyl, Phenyl oder substituiertes Phenyl ist, worin der Substituent C_{1-4}-Alkyl, C_{1-4}-Alkoxy oder Halogen ist;
R^3 Wasserstoff oder Methyl bedeutet;
und R^4 die Bedeutung H aufweist oder eine 4'-(α-L-Oleandrosyl)-α-L-oleandrosyloxy-Gruppe der Formel



ist, unter der Bedingung, daß, falls R^1 H bedeutet und die Doppelbindung fehlt, oder R^4 H ist, R^1 OH ist und die Doppelbindung fehlt, R^2 nicht H oder CH_3 bedeutet.

2. Verbindung nach Anspruch 1, worin R^4 4'-(α-L-Oleandrosyl)-α-L-oleandrosyloxy ist.

3. Verbindung nach Anspruch 2, worin R^2 SR^5 bedeutet und R^5 Methyl oder Ethyl ist.

4. Verbindung nach Anspruch 2, worin R^2 Methyl, Isopropyl oder sek.-Butyl ist.

5. Verbindung nach Anspruch 2, worin R^2 1-(Trifluormethyl)ethyl ist.

6. Verfahren zur Herstellung einer Verbindung der Formel (I) gemäß Anspruch 1, **dadurch gekennzeichnet**, daß es umfaßt das Fermentieren eines Streptomyces avermitilis-Mutantorganismus ATCC 53567 oder 53568, in Gegenwart der geeigneten Carbonsäure der Formel $R^2CH_2CO_2H$, worin R^2 die oben angegebene Bedeutung besitzt, oder eines Salzes, Esters oder Amids davon oder einer oxidativen Vorstufe dafür und Isolieren der Verbindung der Formel I, worin R^1 OH ist und die Doppelbindung fehlt oder worin die Doppelbindung vorhanden ist und R^1 fehlt und R^4 4'-(α-L-Oleandrosyl)-α-L-oleandrosyloxy bedeutet, und, falls gewünscht, Hydrieren des Produkts, worin die Doppelbindung vorhanden ist und R^1 fehlt, um die Verbindungen der Formel (I) zu erhalten, worin die Doppelbindung fehlt und R^1 H bedeutet, oder Hydrolysieren, gefolgt von Halogenierung und Reduktion, um die Verbindungen der Formel (I) zu erhalten, in welchen R^4 H ist.

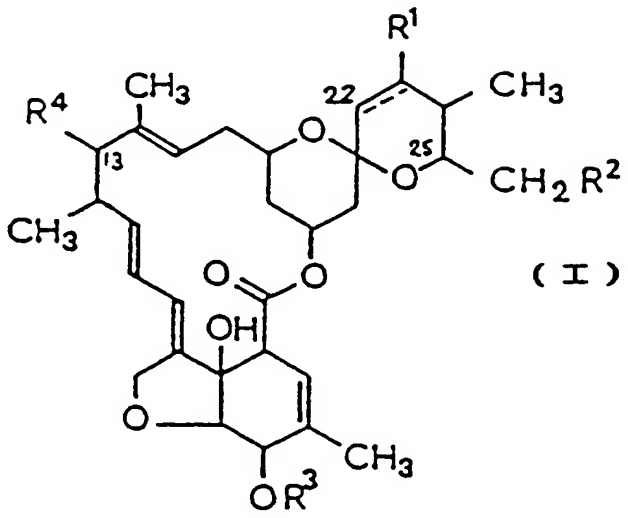
7. Zusammensetzung für die Behandlung und Verhinderung von parasitischen Infektionen bei Menschen und Tieren, einschließend ectoparasiticide, insekticide, akaricide und anthelmintische Zusammensetzungen, welche eine Verbindung der Formel (I), wie sie in irgendeinem der Ansprüche 1 bis 5 beansprucht wird, zusammen mit einem inerten Verdünnungsmittel oder Träger, umfaßt.

8. Zusammensetzung nach Anspruch 7 in Form eines flüssigen Trunks oder einer oralen oder injizierbaren Formulierung oder in Form eines Tierfuttermittels oder einer Vormischung oder einer Ergänzung für den Zusatz zum Tierfutter.

9. Verbindung der Formel I nach einem der Ansprüche 1 bis 5 für die Verwendung in der Behandlung oder der Verhütung von parasitischen Infektionen bei Menschen und Tieren.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung einer Verbindung der Formel:



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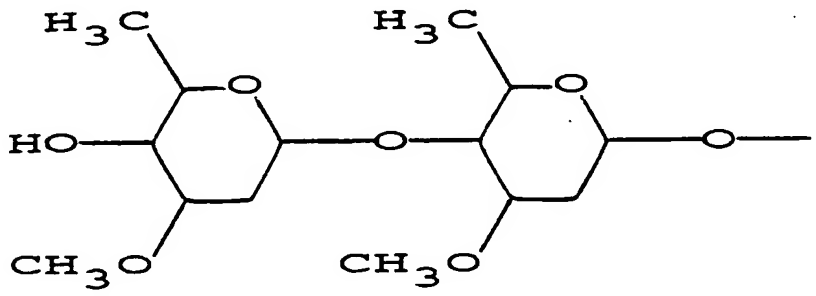
worin die gestrichelte Linie in der 22-23-Stellung eine wahlfreie Doppelbindung bedeutet und worin entweder R^1 die Bedeutung H oder OH aufweist und die Doppelbindung fehlt, oder, worin die Doppelbindung vorhanden ist und R^1 fehlt;
R^2 ist H, C_{1-8}-Alkyl, C_{2-8}-Alkenyl, C_{2-8}-Alkinyl, Alkoxyalkyl oder Alkylthioalkyl mit 1 bis 6 Kohlenstoffatomen in jeder Alkyl- oder Alkoxy-Gruppe, worin irgendeine der Alkyl-, Alkoxy-, Alkenyl- oder Alkinyl-Gruppen durch ein oder mehrere Halogenatome substituiert sein kann; oder eine C_{3-8}-Cycloalkyl- oder C_{5-8}-Cycloalkenyl-Gruppe, wobei jede von beiden gegebenenfalls durch Methylen oder eine oder mehrere C_{1-4}-Alkyl-Gruppen oder Halogenatome substituiert sein kann; oder eine Gruppe der Formel SR^5, worin R^5 C_{1-8}-Alkyl, C_{2-8}-Alkenyl, C_{2-8}-Alkinyl, C_{3-8}-Cycloalkyl, C_{5-8}-Cycloalkenyl, Phenyl oder substituiertes Phenyl ist, worin der Substituent C_{1-4}-Alkyl, C_{1-4}-Alkoxy oder Halogen ist;
R^3 Wasserstoff oder Methyl bedeutet;
und R^4 die Bedeutung H aufweist oder eine 4'-(α-L-Oleandrosyl)-α-L-oleandrosyloxy-Gruppe der Formel



ist, unter der Bedingung, daß, falls R^1 H bedeutet und die Doppelbindung fehlt, oder R^4 H ist, R^1 OH ist und die Doppelbindung fehlt, R^2 nicht H oder CH_3 bedeutet, welches umfaßt das Fermentieren eines Streptomyces avermitilis-Mutantorganismus ATCC 53567 oder 53568, in Gegenwart der geeigneten Carbonsäure der Formel $R^2CH_2CO_2H$, worin R^2 die oben angegebene Bedeutung besitzt, oder eines Salzes, Esters oder Amids davon oder einer oxidativen Vorstufe dafür und Isolieren der Verbindung der Formel I, worin R^1 OH ist und die Doppelbindung fehlt oder worin die Doppelbindung vorhanden ist und R^1 fehlt und R^4 4'-(α-L-Oleandrosyl)-α-L-oleandrosyloxy bedeutet, und, falls gewünscht, Hydrieren des Produkts, worin die Doppelbindung vorhanden ist und R^1 fehlt, um die Verbindungen der Formel (I) zu erhalten, worin die Doppelbindung fehlt und R^1 H bedeutet, oder Hydrolysieren, gefolgt von Halogenie-

rung und Reduktion, um die Verbindungen der Formel (I) zu erhalten, in welchen R^4 H ist.

2. Verfahren nach Anspruch 1, worin R^4 4-(α-L-Oleandrosyl)-α-L-oleandrosyloxy ist und die wahlfreien Hydrolyse-, Halogenierungs- und Reduktions-Stufen nicht durchgeführt werden.

3. Verfahren nach Anspruch 2, worin R^2 SR^5 und R^5 Methyl oder Ethyl ist.

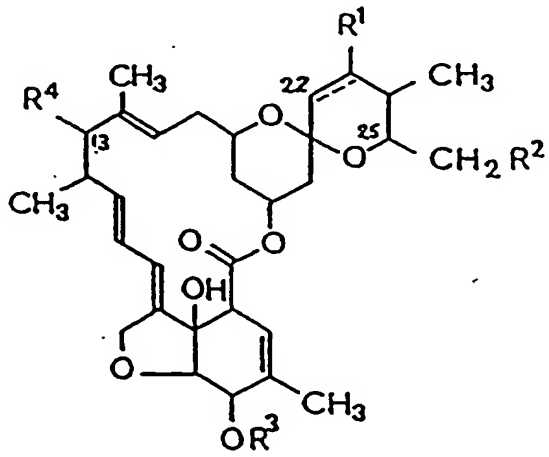
4. Verfahren nach Anspruch 2, worin R^2 Methyl, Isopropyl oder sek.-Butyl ist.

5. Verfahren nach Anspruch 2, worin R^2 1-(Trifluormethyl)ethyl ist.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Composé de formule :



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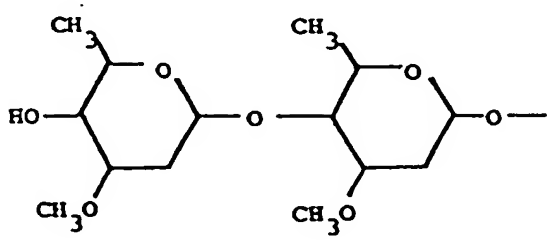
dans laquelle la ligne discontinue en position 22-23 représente une double liaison facultative et dans laquelle R^1 représente H ou un groupe OH et la double liaison est absente, ou bien la double liaison est présente et R^1 est absent ;

R^2 représente H, un groupe alkyle en C_1 à C_8, alcényle en C_2 à C_8, alcynyle en C_2 à C_8, alkoxyalkyle ou alkylthioalkyle contenant 1 à 6 atomes de carbone dans chaque groupe alkyle ou alkoxy, l'un quelconque desdits groupes alkyle, alkoxy, alcényle ou alcynyle pouvant être substitué avec un ou plusieurs atomes d'halogènes ; ou un groupe cycloalkyle en C_3 à C_8 ou cycloalcényle en C_5 à C_8, dont chacun peut être facultativement substitué avec un groupe méthylène ou un ou plusieurs groupes alkyle en C_1 à C_4 ou atomes d'halogènes ; ou un groupe de formule SR^5 dans laquelle R^5 représente un groupe alkyle en C_1 à C_8, alcényle en C_2 à C_8, alcynyle en C_2 à C_8, cycloalkyle en C_3 à C_8, cycloalcényle en C_5 à C_8, phényle ou phényle substitué dans lequel le substituant est un groupe alkyle en C_1 à C_4, alkoxy en C_1 à C_4 ou halogéno ;

R^3 représente l'hydrogène ou un groupe méthyle ;

et R^4 représente H ou un groupe 4'-(alpha-L-oléandrosyl)-alpha-L-oléandrosyloxy de formule :



sous réserve que, lorsque R^1 représente H et la double liaison est absente, ou bien R^4 représente H, R^1 représente un groupe OH et la double liaison est absente, R^2 ne représente pas H ou un groupe CH_3.

2. Composé suivant la revendication 1, dans lequel R^4 représente un groupe 4'-(alpha-L-oléandrosyl)-alpha-L-oléandrosyloxy.

3. Composé suivant la revendication 2, dans lequel R^2 représente un groupe SR^5 et R^5 représente un groupe méthyle ou éthyle.

4. Composé suivant la revendication 2, dans lequel R^2 représente un groupe méthyle, isopropyle ou sec-butyle.

5. Composé suivant la revendication 2, dans lequel R^2 représente un groupe 1-(trifluorométhyl)éthyle.

6. Procédé de préparation d'un composé de formule (I) suivant la revendication 1, qui consiste à faire fermenter un organisme mutant Streptomyces avermitilis ATCC 53567 ou 53568, en présence de l'acide carboxylique approprié de formule $R^2CH_2CO_2H$, dans laquelle R^2 répond à la définition précitée, ou d'un de ses sels, esters ou amides ou bien d'un précurseur oxydatif d'un tel composé, et à isoler le composé de formule (I) dans laquelle R^1 représente un groupe OH et la double liaison est absente ou dans laquelle la double liaison est présente et R^1 est absent et R^4 représente un groupe 4'-(alpha-L-oléandrosyl)-alpha-L-oléandrosyloxy et, si cela est désiré, à hydrogéner le produit dans lequel la double liaison est présente et R^1 est absent pour obtenir les composés de formule (I) dans laquelle la double liaison est absente et R^1 représente H, ou bien à effectuer une hydrolyse suivie par une halogénation et une réduction pour obtenir les composés de formule (I) dans laquelle R^4 représente H.

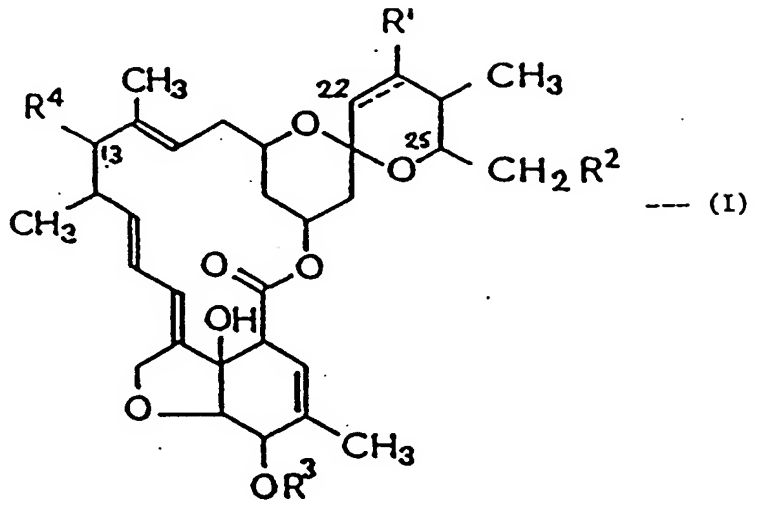
7. Composition pour le traitement et la prévention d'infections parasitaires chez l'homme et les animaux, consistant en une composition ectoparasiticide, insecticide, acaricide ou anthelminthique, qui comprend un composé de formule (I) suivant l'une quelconque des revendications 1 à 5 en association avec un diluant ou support inerte.

8. Composition suivant la revendication 7 sous forme d'un breuvage liquide ou d'une formulation orale ou injectable, ou bien sous forme d'un aliment, prémélange ou supplément pour animaux, destiné à être ajouté à la nourriture d'un animal.

9. Composé de formule (I) suivant l'une quelconque des revendications 1 à 5, destiné à être utilisé dans le traitement ou la prévention d'infections parasitaires chez l'homme et les animaux.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé de préparation d'un composé de formule :



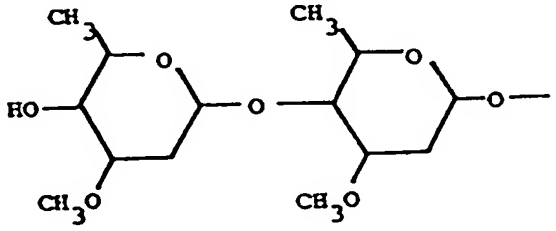
--- (I)

dans laquelle la ligne discontinue en position 22-23 représente une double liaison facultative et dans laquelle R^1 représente H ou un groupe OH et la double liaison est absente, ou bien la double liaison est présente et R^1 est absent ;

R^2 représente H, un groupe alkyle en C_1 à C_8, alcényle en C_2 à C_8, alcynyle en C_2 à C_8, alkoxyalkyle ou alkylthioalkyle contenant 1 à 6 atomes de carbone dans chaque groupe alkyle ou alkoxy, n'importe lequel desdits groupes alkyle, alkoxy, alcényle ou alcynyle pouvant être substitué avec un ou plusieurs atomes d'halogènes ; ou un groupe cycloalkyle en C_3 à C_8 ou cycloalcényle en C_5 à C_8, dont chacun peut être substitué facultativement avec un groupe méthylène ou un ou plusieurs groupes alkyle en C_1 à C_4 ou atomes d'halogènes ; ou un groupe de formule SR^5 dans laquelle R^5 représente un groupe alkyle en C_1 à C_8, alcényle en C_2 à C_8, alcynyle en C_2 à C_8, cycloalkyle en C_3 à C_8, cycloalcényle en C_5 à C_8, phényle ou phényle substitué dans lequel le substituant est un groupe alkyle en C_1 à C_4, alkoxy en C_1 à C_4 ou halogéno ;

R^3 représente l'hydrogène ou un groupe méthyle ;

et R^4 représente H ou un groupe 4'-(alpha-L-oléandrosyl)-alpha-L-oléandrosyloxy de formule :



sous réserve que, lorsque R^1 représente H et la double liaison est absente, ou R^4 représente H, R^1 représente un groupe OH et la double liaison est absente, R^2 ne représente pas H ou un groupe CH_3, qui consiste à faire fermenter un organisme mutant Streptomyces avermitilis ATCC 53567 ou 53568, en présence de l'acide carboxylique approprié de formule $R^2CH_2CO_2H$, dans laquelle R^2 répond à la définition précitée, ou un de ses sels, esters ou amides ou un précurseur oxydatif d'un tel composé, et à isoler le composé de formule (I) dans laquelle R^1 représente un groupe OH et la double liaison est absente ou dans laquelle la double liaison est présente et R^1 est absent et R^4 représente un groupe 4'-(alpha-L-oléandrosyl)-alpha-L-oléandrosyloxy, et, si cela est désiré, à hydrogéner le produit dans lequel la double liaison est présente et R^1 est absent pour obtenir les composés de formule (I) dans laquelle la double liaison est absente et R^1 représente H, ou à effectuer une hydrolyse suivie par une halogénation et une réduction pour obtenir les composés de formule (I) dans laquelle R^4 représente H.

2. Procédé suivant la revendication 1, dans lequel R^4 représente un groupe 4'-(alpha-L-oléandrosyl)-alpha-L-oléandrosyloxy, et les étapes facultatives d'hydrolyse, d'halogénation et de réduction ne sont pas mises en oeuvre.

3. Procédé suivant la revendication 2, dans lequel R^2 représente un groupe SR^5 et R^5 représente un groupe méthyle ou éthyle.

4. Procédé suivant la revendication 2, dans lequel R^2 représente un groupe méthyle, isopropyle ou sec-butyle.

5. Procédé suivant la revendication 2, dans lequel R^2 représente un groupe 1-(trifluorométhyl)éthyle.